

CLAIMS

We claim:

1. A non-naturally occurring IA protein comprising an amino acid sequence which comprises substitution of at least one amino acid residue when compared to an amino acid sequence of a naturally occurring human insulin and wherein said IA protein has an altered property when compared to the same property of human insulin and binds to a cell comprising an insulin receptor.

2. A non-naturally occurring IA protein according to claim 1, wherein said IA protein comprises a substitution at a position selected from the group consisting of positions A3, A5, A6, A7, A11, A15, A16, A19, A20, B2, B7, B15, B19, and B22.

3. A non-naturally occurring IA protein according to claim 2, wherein substitution is selected from the group of A7-S, A7-E, B2-E, B2-T, B4-Y, B7-Y, B4-F, B7-Y, B7-E, and B7-D.

4. A non-naturally occurring IA protein according to claim 1, wherein said IA protein comprises substitutions of at least four amino acid residues.

5. A non-naturally occurring IA protein conformer having a three dimensional backbone structure that substantially corresponds to the three dimensional backbone structure of human insulin, wherein the amino acid sequence of said conformer and said amino acid sequence of said human insulin are less than about 98% identical.

6. A non-naturally occurring IA protein comprising at least one amino acid substitution as compared to human insulin, wherein at least one of said substitutions is selected from the amino acid residues at positions selected from positions B5 and B14, and wherein said IA protein forms a hexamer in the absence of a phenolic preservative.

7. The non-naturally occurring IA protein according to claim 6, wherein said IA protein comprises a substitution selected from the group of B5-F, B5-W, B14-F, B14-W, B14-Y, and B14-I.

8. The non-naturally occurring IA protein according to claim 1, wherein said IA protein comprises At least 5 substitution at positions selected from the group consisting of positions A1, A10, A16, A17, A19, B1, B2, B4, B8, B11, B12, B14, B25, B26, B27 and B28.

9. The non-naturally occurring IA protein according to claim 8, wherein said substitutions are selected from the group of substitutions consisting of A1-N, A10-Q, A16-Y, A17-Y, A19-F, B1-D, B2-K, B4-F, B8-L, B11-I, B12-R, B14-W, B25-N, B26-F, B27-D, and B28-N.

5 10. The non-naturally occurring IA protein according to claim 1 wherein said IA protein comprises an amino acid sequence selected from the group of amino acid sequences shown in Figure 3A, Figure 3B, Figure 3C, Figure 3D, Figure 3E, Figure 3F, Figure 3G, Figure 4A, Figure 4B, Figure 4C, Figure 4D, Figure 4E, Figure 4F, Figure 4G, Figure 5A, Figure 5B, and Figure 5C (SEQ ID NOS:7-23).

11. A recombinant nucleic acid encoding the non-naturally occurring IA protein of claim 1 or 10.

12. An expression vector comprising the recombinant nucleic acid of claim 11.

10 13. A host cell comprising the recombinant nucleic acid of claim 11.

14. A host cell comprising the expression vector of claim 12.

15. A method of producing a non-naturally occurring IA protein comprising culturing the host cell of claim 13 under conditions suitable for expression of said nucleic acid.

16. The method according to claim 15 further comprising recovering said IA protein.

15 17. A pharmaceutical composition comprising an IA protein according to claim 1 or 10 and a pharmaceutical carrier.

18. A method for treating an insulin responsive condition comprising administering an IA protein according to claim 1 or 10 to a patient in need thereof.

19. The method according to claim 18, wherein said condition is a disorder of carbohydrate metabolism.

20 20. The method according to claim 18, wherein said condition is type 1 diabetes.

21. The method according to claim 22, wherein said condition is type 2 diabetes.